REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the claims. Applicants respectfully request reconsideration and withdrawal of the claim objections and pending rejections under obviousness-type double patenting and 35 U.S.C. §§ 102(b), 103(a), and 112, first and second paragraphs.

Status of the Claims

Please cancel claims 24, 28, 31, 36, and 41 without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in one or more continuation applications.

Applicants have amended claims 23, 25-27, 29-30, 32-35, 37, 39-40, 42, and 44 to clarify the claimed subject matter. Support can be found throughout the specification, including at page 10, lines 21-27; page 19, lines 17-20; and page 52, lines 6-17. Claims 40 and 42 have been amended to correct the dependency in view of the cancellation of claim 36.

Applicants have added new claims 49-51. Support can be found throughout the specification, including at page 10, lines 21-27; page 28, line 6-33; page 29, lines 3-5, page 36, lines 14-17, and page 43, lines 3-22. New claim 49 depends on claim 35 and falls within the election of species. New claim 50 is similar to claim 25. New claim 51 is similar to claim 23. Upon entry of this amendment, claims 23, 25-27, 29-30, 32-35, 37-40, and 42-50 will be pending with claims 26-27, 29, 32, 34, 36-37, 40-42, and 50 withdrawn.

IDS

In the Office Action, the Examiner indicated that the IDS filed on 7/20/06 was identical to that filed on 12/08/03. Applicants disagree. Applicants provide a courtesy copy of the IDS as downloaded from PAIR. Applicants request consideration of the references and return of the initialed 1449 form.

Claim Objections

1. Claim 24. The Examiner objects to claim 24 for inappropriate parentheses around "SEQ ID NO:13". Applicants have cancelled claim 24 rendering the objection of this claim moot.

2. Claims 23, 28-31, and 33. The Examiner objects to claims 23, 28-31, and 33 because the status identifier is misspelled. Applicants have cancelled claim 28 rendering the objection of this claim moot. Applicants have corrected these obvious typographical errors in claim 23, 30-31, and 33.

3. Claim 31. The Examiner objects to claim 31. Applicants have cancelled claim 31. As such, this objection is now moot.

4. Claim 44. The Examiner objects to claim 44 and asserts that a nucleic acid does not further limit the protein it encodes. Applicants have amended claim 44 to recite "[a]n isolated nucleic acid comprising a modified nucleic acid sequence that encodes a modified thrombopoietin according to claim 35..." Support for amended claim 44 can be found throughout the specification, including at page 32, lines 18-30 and at page 40, line 7 to page 41, line 6.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the claim objections.

Double Patenting

The Examiner rejects claims 30 and 31 based on the judicial doctrine of obviousness-type double patenting as allegedly unpatentable over claims 11-12, 25, and 25 [sic] of U.S. Patent No. 6,673,580, the parent application of the instant application. Claim 31 has been cancelled rendering the rejection of this claim moot. Applicants request clarification concerning the recitation of claim 25 twice in the rejection. Applicants acknowledge the Examiner's rejection of claim 30 for double patenting. Applicants request that this rejection be held in abeyance until notice of allowable subject matter.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 23, 28, 33, 35, 38 and 43-48 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claim 28 has been cancelled rendering the rejection of this claim moot. Applicants respectfully traverse this rejection with respect to the remainder of the rejected claims.

Compliance with the written description requirement does not require an applicant to describe exactly the subject matter claimed; rather, the description must clearly allow a person of ordinary skill in the art to recognize that he or she invented what is claimed. *Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563 (Fed. Cir. 1991). The test is whether the originally filed specification reasonably conveys to a person having ordinary skill in the art that applicant had possession of the subject matter later claimed. *In re Kaslow,* 707 F.2d 1366 (Fed. Cir. 1991). **Examples are not required to meet the written description requirement.** *Falkner v. Inglis*, 448 F.3d, 1357, 1366 (Fed. Cir. 2006).

The written description requirement must be applied in the context of the particular invention and state of the knowledge. *Capon v. Eshhar*, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). It is unnecessary to spell out every detail of the invention in the specification. Only enough must be included to convince a person of skill in the art that the inventor possessed the invention. *Falkner v. Inglis*, No. 05-1234, slip. op. at 14 (Fed Cir. May 26, 2006) (citing *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.,* 424 F.3d 1336, 1345 Fed. Cir. 2005).

Applying these standards, Applicants submit the specification sufficiently describes the claimed genus of polypeptides. The Examiner has acknowledged that Applicants have patented a method of making such variants as described. This method applies to any polypeptide. In the instant application, Applicants have exemplified this method and the claimed polypeptides with the genus of TPO polypeptides (Examples 3-6 at pages 50-59). Applicants respectfully assert that there is no requirement to describe each and every possible variant or each and every possible therapeutic polypeptide. Applicants respectfully assert that based on the described method and the TPO examples at pages 50-59, a person of skill in the art would understand that Applicants were in possession of the claimed subject matter.

The claim in the case *Falkner v. Inglis*, No. 05-1234, slip. op. at 14 (Fed Cir. May 26, 2006)is illustrative:

"Claim 1 of the Falkner '212 patent reads: A vaccine comprising (a) a defective poxvirus that lacks a function imparted by an essential region of its parental poxvirus, wherein (i) said defective poxvirus comprises a DNA polynucleotide encoding an antigen and said DNA polynucleotide is under transcriptional control of a promoter, and (ii) the function can be complemented by a complementing source; and (b) a pharmaceutically acceptable carrier."

In this case, the Federal Circuit found that examples, actual reduction to practice, and recitation of known structure was not required for the claim to satisfy written description. Claim 23 as presented by Applicants is similar to the claim of that case. Applicants submit that the structures of therapeutic polypeptides are known or readily obtainable. Claim 23 now indicates that immunodominant epitopes are epitopes that bind to antibodies from a naive animal or human. Modification occurs in the immunodominant epitope to reduce immunogenicity and retain a substantial therapeutic activity, which can be readily determined. Thus, Applicants submit that the specification provides written description of claims 23 and 33 .

Regarding claims 35, 38, and 43-48, the Examiner alleges that the description is not commensurate in scope with the claims. Applicants disagree.

Applicants respectfully assert that claims to the modification of amino acids 333-353 of SEQ ID NO:13 and the subset of amino acids 338-353 are adequately described in the specification. Example 4, specifically at page 52, lines 6-17, describes a method of predicting epitopes. The model predicted an epitope based on class II MHC binding motifs at amino acids 312-331 of the mature TPO (TPTSPLLNTSYTHSQNLSQE (SEQ IN NO:2)). This corresponds to 333-353 of SEQ ID NO:13, the full-length TPO. Applicants identify an immunodominant epitope including amino acids 318 to 332 (SEQ ID NO:1) of the mature TPO (page 19, lines 17-20), which is a subset of the amino acid sequence of the predicted epitope from Example 4. The Examiner must explain why he/she doubts the truth or accuracy of the specification. *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971); MPEP §21640.04. The Examiner has not refuted that SEQ ID NO:2 is an immunodominant epitope of TPO. For at least these reasons, Applicants assert that the epitope is fully described in context of the scope of the claims.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112. first paragraph.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 23, 25, 28, 30-31, 33, 35, 38-39 and 43-48 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The second paragraph of 35 U.S.C. § 112 sets forth two requirements:

A) the claims must set forth the subject matter that applicants regard as their invention; and

B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. MPEP § 2171.

Claims 28 and 31 have been cancelled rendering the rejection of these claims moot. Applicants respectfully traverse these rejections with respect to the remainder of the claims.

1. Claim 23. The Examiner rejects claim 23 and asserts that the claim is a concept rather than a particular polypeptide or set of polypeptides. Applicants respectfully disagree.

Applicants have claimed a modified therapeutic polypeptide, wherein the polypeptide is modified in an immunodominant epitope and wherein the modified polypeptide induces a reduced immune response compared to the unmodified polypeptide while retaining a substantial therapeutic activity of the polypeptide. Applicants submit that the metes and bounds of claim 23 are clearly defined.

The structure and function of therapeutic polypeptides are known to those of skill in the art or can be readily determined. Applicants claim 23 now refers to an immunodominant epitope that binds to an antibody or population of antibodies obtained from a naive human or animal or population thereof . A representative polypeptide, TPO, has been described. Applicants understand that the Examiner is rejecting this claim due to its breadth. Breadth of a claim is not equated with indefiniteness. *In re Miller*, 441 F.2d 689 (CCPA 1971); MPEP 2173.04. Additionally, U.S. patent law does not require an actual reduction to practice or working examples. *Falkner v. Inglis*, 448 F.3d, 1357, 1366 (Fed. Cir. 2006). For at least these reasons, Applicants respectfully request removal of this rejection.

2. Modified. The Examiner contends that the recitation of the term "modified" indicates that there was a "starting" polypeptide that has been altered to conform with the claimed limitations (Office Action at page 4). While not acquiescing to the rejection and solely to expedite prosecution, the claims now refer to modification of an unmodified therapeutic polypeptide. Applicants have amended claims 26-27, 29-30, and 33 to recite the term "therapeutic" in conjunction with the term "polypeptide". Support can be found throughout the specification, including at page 4, lines 11-18 and 24-28; page 8, lines 6-15; and page 14, lines 7-

12. Upon entry of the amendment, all of the claims will refer, directly or indirectly, to either a "therapeutic polypeptide" or "thrombopoietin", which is a species of therapeutic polypeptide. Thus, the "therapeutic polypeptide", whether thrombopoietin or another therapeutic polypeptide, is the reference polypeptide to be modified to arrive at the modified polypeptide or modified thrombopoietin in the instant claims. Applicants respectfully assert that the terms "therapeutic polypeptide" or "thrombopoietin" provide sufficient definiteness as the starting polypeptide of the instant claims.

*3. **Modification Only in an Immunodominant Epitope.*** The Examiner asserts that "modification only in an immunodominant epitope" is indefinite. The Examiner questions whether "only in an immunodominant epitope" excludes amino acids not in the epitope, particularly in intervening sequence of discontinuous epitopes. Applicants assert that the plain and ordinary language of the claim is clear. The modification only occurs in the epitope. Intervening sequence is not in the epitope, and therefore would be excluded from modification.

The Examiner further questions deletion of an entire immunodominant epitope. "[I]f, for example, residues 339-353 *are* an immunodominant epitope, it is not clear how deletion of that entire sequence could be construed as a modification in that immunodominant epitope." [emphasis in original] (sentence spanning pages 4 and 5 of the Office Action). Applicants respectfully disagree and asserts that it is plainly described in the specification. At page 19, lines 17-20, the specification describes that amino acids LNTSYTHSQNLSQEG (SEQ ID NO:1), which are amino acids 318 to 332 of the mature TPO, are included in an immunodominant epitope. The term "modification" is defined at page 10, lines 21-27 as

> ... at least one change in an immunodominant epitope in a polypeptide and/or a nucleic acid encoding such a polypeptide. The change in the immunodominant epitope reduces an immune response to the polypeptide, especially the antibody response, while retaining a substantial therapeutic activity. Changes **can include one or more** deletions, additions, substitutions in an epitope, as well as chemical modifications to the amino acids in an epitope such as glycosylation, and pegylation of the amino acids. [**emphasis added**]

By definition, a deletion of SEQ ID NO:1 would be a deletion modification in an immunodominant epitope of TPO. This modification is only in the immunodominant epitope. Applicants respectfully assert that in view of the specification and the plain and ordinary

language of the claims, "modification only in an immunodominant epitope" is sufficiently definite.

4. Claim 25. The Examiner rejects claim 25 and asserts the use of "an" renders the claim indefinite. While not acquiescing to the rejection and solely to expedite prosecution, Applicants have amended claim 25 to address the rejection.

5. Claim 30. a) The Examiner asserts that claim 30 is an incomplete method claim. First the Examiner contends that no method steps are recited to identify an immunodominant epitope. Applicants respectfully assert that this is not necessary. Claim 30 recites the step of "identifying at least one immunodominant epitope in the polypeptide". There multiple ways to achieve this method step. Applicants have described different methods of identifying an immunodominant epitope at page 13, line 29 to page 14, line 4; at page 18, lines 5-12; and at page 21, lines 27-28. For at least this reason, the step is well defined and supported by the specification.

b) The Examiner also asserts that the recitation of "reduces an immune response" is a relative limitation. Applicants have amended claim 30 to recite "compared to the unmodified polypeptide."

6. Claim 35. The Examiner asserts that the recitation of "native" is indefinite. The Examiner states that the "term could indicate having a "native" sequence, or alternatively that the protein is not denatured." The term "native sequence" is expressly described at page 9, lines 5-10:

> A "native sequence" polypeptide means a polypeptide having the same amino acid sequence of the polypeptide derived from nature and encompasses all naturally occurring forms of the polypeptide such as truncated forms, secreted forms, variant forms and naturally occurring allelic variants. A native sequence polypeptide can be isolated from nature or produced by recombinant or synthetic means. A native amino acid sequence for human thrombopoietin is provided in WO 95/18858.

The Examiner also asserts that "not all "native" TPO sequences have been discovered or characterized" so a skilled person could not determine a "native sequence". Applicants submit that since a reference sequence is provided in the application as well as a characterization of the functional activity thrombopoeitin, one of skill in the art would readily be able to identify a native sequence. For at least these reasons, Applicants respectfully assert that the term "native" is described and request removal of this rejection.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102(b)

The Examiner rejects the following claims under 35 U.S.C. § 102 (b) --1) claims 23, 28, 30-31, and 33 as allegedly anticipated by WO 92/10755 (Lovborg et al.); 2) claims 23, 28, 33, 35, 38 and 43-48 as allegedly anticipated by U.S. Patent No. 5,641,655 (Foster et al.); and 3) claims 23, 25, 28, 33, 35, 38 and 43-48 as allegedly anticipated by U.S. Patent No. 6,608,183 (Cox et al.). Claims 28 and 31 have been cancelled rendering the rejection of these claims moot. Applicants respectfully traverse this rejection with respect to the remainder of the claims.

As an initial matter, at the top of page 10 of the Office Action, there is a sentence that starts mid-sentence. Since there is also blank space above these statements, it appears that this "rejection" is incomplete. Although it appears under the heading of "Claim Rejections – 35 USC § 102", it appears to be an obviousness rejection or related to an obviousness rejection. Applicants acknowledge the Examiner's statements and parts thereof, but ask for clarification. It is not stated which claims are rejected and why.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); *See also*, MPEP §2131. The Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the prior art. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original); MPEP § 2112. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citations omitted); MPEP § 2112. Applicants respectfully assert that each of WO 92/10755, U.S. Patent No. 5,641,655, and U.S. Patent No. 6,608,183 fail to disclose, expressly or inherently, each and every element of the instant claims.

Applicants claim 23 is directed to a modified therapeutic polypeptide having a modification only in an immunodominant epitope of the unmodified therapeutic polypeptide, wherein the immunodominant epitope is an epitope that is recognized by an antibody or population of antibodies obtained from a naive human or animal or population thereof, wherein the modification reduces an immune response to the polypeptide compared to the unmodified therapeutic polypeptide while retaining a substantial therapeutic activity of the unmodified therapeutic polypeptide, wherein the modification is a deletion, substitution, or chemical modification of at least one amino acid.

Applicants' claim 35 is directed to a modified native thrombopoietin comprising at least one modification only of amino acids of SEQ ID NO:2 of native thrombopoietin, wherein the modification reduces the immune response to thrombopoietin while retaining a substantial therapeutic activity of thrombopoietin, wherein the modification is a deletion, substitution, or chemical modification of at least one amino acid.

1. WO 92/10755. The Examiner rejects claims 23, 28, 30-31, and 33 as anticipated by WO 92/10755. Claim 23 recites a modified therapeutic polypeptide having a **modification only in an immunodominant epitope**, wherein the immunodominant epitope is an epitope that is recognized by an antibody or population of antibodies obtained from a naive human or animal or population thereof,...[emphasis added]. Claims 28 and 33 depend on claim 23. Claim 30 recites a method...comprising a) identifying at least one immunodominant epitope...wherein only the immunodominant epitope is modified. Claim 31 has been cancelled. Applicants respectfully assert that WO 92/10755 does not disclose identifying an immunodominant epitope or modifying a polypeptide only in its immunodominant epitope, wherein the immunodominant epitope is an epitope that is recognized by an antibody or population of antibodies obtained from a naive human or animal or population thereof.

The Examiner states at page 8 that "Lovborg et al. disclose a method of mapping immunodominant epitopes of desired proteins..." The Examiner then cites the abstract and claims 1, 5, 6, 18, and 19 to support this statement. However, nowhere in the abstract or claims, or even the specification, do Lovborg et al. disclose identifying an immunodominant epitope and modifying a therapeutic protein only in an immunodominant epitope. The specification only identifies any epitope and does not particularly point to immunodominant epitopes. An

"immunodominant epitope" is specifically described in the specification at page 7, lines 7-10. An immunodominant epitopes distinguishable from an "epitope", which is defined in the specification at page 6, line 24 to page 7, line 6.

Additionally, Lovborg et al. do not disclose that the only modification to the amino acid sequence occurs in the immunodominant epitope. In addition, Loveberg does not describe an immunodominant epitope that is recognized by an antibody or population of antibodies form a naïve human or animal.

Applicants respectfully assert that Lovborg et al. do not disclose the instant claim elements of identifying immunodominant epitopes or making amino acid modifications to immunodominant epitopes. For at least these reasons, Lovborg et al. do not disclose each and every claim element, and thus, do not anticipate the claims.

2. U.S. Patent No. 5,641,655. The Examiner cites the '655 patent as disclosing a truncation variant of TPO that includes the deletion of residues 339-353 of the full-length TPO polypeptide. Specifically, the Examiner cites col. 1, ll. 50-67 as evidence of anticipation of claims 23, 28, 30-31, and 33. Applicants respectfully traverse this rejection.

The '655 patent does not disclose modification of thrombopoietin only in an immunodominant epitope. There is no discussion in this reference of reducing immunogenicity or identifying immunodominant epitopes. This reference does not describe an immunodominant epitope of TPO that is recognized by an antibody or population of antibodies obtained from a naive human or animal or population thereof.

With respect to claim 35, the '655 patent does not disclose modification only of amino acids of SEQ ID NO:2 of native thrombopoietin, wherein the modification reduces the immune response to thrombopoietin while retaining a substantial therapeutic activity of thrombopoietin. There is no discussion in this reference of immunodominant epitopes or reducing immunogenicity of TPO.

For at least these reasons, the '655 patent does not disclose each and every claim element, which thereby fails the requirements under 35 U.S.C. § 102(b) to anticipate the claims.

3. U.S. Patent No. 6,608,183. The Examiner cites the '183 patent as disclosing the introduction of cysteine residues from amino acids 312-332 of the mature TPO. The Examiner

also cites the '183 patent for disclosing TPO truncated between amino acids 147 and 332. In view of the amendments, the '183 patent does not disclose each and every element of the claims.

The instantly amended claims require that the modification be a deletion or a substitution. The '183 patent requires insertions of cysteine residues into TPO (col. 34, lines 20-32). The truncations of TPO disclosed by the '183 patents are not simply a truncation of TPO from a certain amino acid residue. Rather, TPO is truncated in conjunction with a cysteine insertion (col. 34, lines 35-43). Additionally, the '183 patent does not demonstrate any variant that induces a reduced immune response while retaining a substantial therapeutic activity of TPO. For at least these reasons, the TPO variants disclosed in the '183 patent are not encompassed by the instant claims and thereby do not anticipate.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b).

Rejections under 35 U.S.C. § 103(a)

The Examiner rejects claim 39 under 35 U.S.C. § 103(a) as allegedly obvious over Cox et al. (U.S. Patent No. 6,608,183). Applicants respectfully traverse the rejection.

As an initial matter, Applicants request clarification of this rejection as the Examiner only rejects claim 39 as obvious. Claim 39 depends on claim 38, which depends on claim 35, but neither claim 35 nor claim 38 have been rejected as obvious. A dependent claim is not obvious if the claim from which it depends is not obvious. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988).

Second, the Examiner asserts that Cox et al. teaches a truncation variant of TPO, wherein the C-terminus of TPO is truncated somewhere from amino acid 147 to the terminal amino acid of 332 (which corresponds to amino acid 353 in the instant application). The Examiner further contends from that teaching and the limited number of places for truncation, claim 39 is obvious. Applicants respectfully disagree.

The truncations of TPO disclosed by the '183 patents are not simply a truncation of TPO from a certain amino acid residue. Rather, TPO is truncated in conjunction with a cysteine insertion (col. 34, lines 35-43). To exclude the cysteine insertions would render the TPO variant of the '183 patent unsatisfactory for its intended purpose. The cysteine residues are required (col. 2, lines 29-65 and col. 9, lines 1-55). The patentees used the inserted cysteine residues to

provide conjugation and pegylation sites. "If [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1994); MPEP 2143.01(V). Since removing the cysteine insertions would render the variant polypeptides unsatisfactory for its intended purpose, there is no suggestion or motivation to make this modification of the '183 patent. To make a *prima facie* case of obviousness, "it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007). Without a motivation or suggestion as to modify the cited prior art, the Examiner has not established a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Summary

Applicants submit that the claims of the present application are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative at the telephone number listed below, if the Examiner believes that doing so will advance prosecution.

Respectfully submitted,

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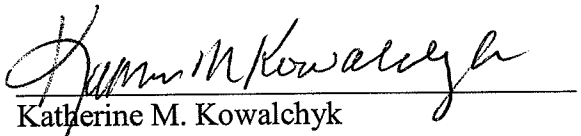

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